REMARKS

Claims 122, 178 and 185-232 are pending, with claims 122, 185, 189, 192, 197, 200, 221-224, 226 and 228-232 being under consideration. Claim 178 is withdrawn as directed to a non-elected invention, and claims 186-188, 190, 191, 193-196, 198, 199, 225 and 227 are withdrawn as directed to non-elected species.

Claim 228 has been amended to further clarify Applicants' claimed invention. Support for such amendment can be found in the specification as originally filed at, for example, page 19, lines 33-35. Claims 202, 203 and 206 have been amended solely to correct typographical errors. No new matter has been added.

I. THE REJECTIONS UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

In the non-final Office Action dated May 11, 2009 ("Office Action"), the Examiner has rejected claims 122, 185, 189, 192, 197, 200, 221-222, 224, 226 and 228-232 under 35 U.S.C. § 103 as unpatentable over U.S. Patent No. 6,329,140 to Lockhart ("Lockhart"), Bowtell, 1999, Nature Genetics Supplement 21:25-32 ("Bowtell"), U.S. Patent No. 6,013,436 to Hui *et al.* ("Hui"), and Ashe et al., 1997, Genes & Development 11:2494-2509 ("Ashe"). The Examiner also has rejected claim 223 as obvious over Lockhart, Bowtell, Hui, and Ashe, and further in view of Schena *et al.*, 1996, Proc. Natl. Acad. Sci. U.S.A. 93:10614-19 ("Schena"). Applicants respectfully disagree with the rejections, for the reasons discussed below.

A. Legal Standard

In *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 U.S.P.Q. 1385 (2007), the Supreme Court stated that the following factors set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966) still control an obviousness inquiry: (1) the scope and content of the prior art; (2) the differences between the prior art and the claimed invention; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *KSR*, 127 S.Ct. at 1734, 82 U.S.P.Q.2d at 1388 (quoting *Graham*, 383 U.S. at 17-18, 14 U.S.P.Q. at 467).

In order to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974). Additionally, the Supreme Court, in *KSR*, affirmed that "a

patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art," and that it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does...because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *KSR*, S.Ct. at 1741, 82 U.S.P.Q.2d at 1396. In addition, under *KSR*, "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions." *KSR*, S.Ct. at 1740, 82 U.S.P.Q.2d at 1396.

Further, hindsight should be avoided in applying the nonobviousness requirement. *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1 U.S.P.Q.2d 1593 (Fed. Cir. 1987), *cert. denied*, 481 U.S. 1052 (1987). "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir. 1988). Moreover, a recent post-*KSR* Federal Circuit decision explained that a non-rigid "flexible TSM test remains the primary guarantor against a non-statutory hindsight analysis" and assures that the obviousness test proceeds on the basis of evidence that arise before the time of invention as the statute requires. *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358, 1364-65 (Fed. Cir. 2008) (citing *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

Finally, in determining the differences between the prior art and the claims, the question under 35 U.S.C. § 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. M.P.E.P. 2141.02 (I), 8th Edition August 2001 (Revision of July 2008) (citing from *Schenk v. Norton Corp.*, 713 F.2d 782, 218 U.S.P.Q. 698 (Fed. Cir. 1983)). Also, the reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 U.S.P.Q. 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). It is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 U.S.P.Q. 769, 779 (Fed. Cir. 1983). A proposed modification that renders a prior art invention inoperable for its intended purpose cannot support an obviousness rejection. *See In re Gordon*, 773 F.2d 900, 221 U.S.P.Q. 1125 (Fed. Cir. 1984). *See also* MPEP 2143.01 (V), 8th Edition August 2001 (Revision of July 2008).

B. Independent Claim 122 and Claims 185, 189, 192, 197, 200, 221, 222, 224, 226, and 228-232 Depending Therefrom Are Patentable Over Lockhart, Bowtell, Hui and Ashe.

Applicants respectfully disagree with the Examiner's rejection. In this response, Applicants (i) explain the nature of Applicants' claimed invention, (ii) articulate why one of ordinary skill in the art would not have combined the cited references to arrive at Applicants' claimed invention, and (iii) clarify why Applicants' specification, and not the disclosures of Lockhart, Bowtell, Hui and Ashe, provides the only common sense reason to combine the claimed elements in the manner recited in Applicants' claims.

The presently claimed invention relates to positionally-addressable ordered arrays of polynucleotide probes bound to a solid support, wherein the polynucleotide probes comprise at least 100 polynucleotide probes of different nucleotide sequences, each said different nucleotide sequence comprising a sequence complementary and hybridizable to a different genomic sequence of the same species of organism, wherein the respective genomic sequences complementary and hybridizable to the probes are found at sequential sites in the genome. The claimed arrays are characterized by the following three essential features: (1) a high density of the genomic sequences complementary to probes in the genome (because the distance between 5′ ends of the sequential sites is always less than 500 bp), (2) a large span of the genomic sequences (because the genomic sequences complementary and hybridizable to the probes span a genomic region of at least 25,000 bp), and (3) at least two probes complementary and hybridizable to genomic sequences contained entirely within an intron (which intron can be the same intron or different introns for the respective at least two probes) ("Exclusively Intron Probes"). In addition, the claimed arrays are characterized as being positionally-addressable ordered arrays, *i.e.*, each probe of the array is located at a known, predetermined position on the solid support in an ordered fashion such that the identity (*i.e.*, the sequence of each probe) can be determined from its position on the array, and thus hybridization of the array to the target mRNA or cDNA molecule yields a map of expressed sequences in a portion of the genome.

The above-recited elements of the claimed arrays were combined to create a high-throughput array for precisely mapping respective positions of the expressed genes and identifying the structure of such genes, *e.g.*, relative locations of exon and intron sequences within genes, in genomic sequences that are spread over large regions of genomic DNA. The

mapping of genes in the genome and the determination of the structure of genes is performed by contacting the claimed positionally-addressable ordered arrays with a labeled mRNA or a cDNA molecule that hybridizes to probes on the array corresponding to the locations of exons, thereby detecting sequences expressed in a given biological sample. Thus, hybridization of mRNA or cDNA to exon probes will yield a positive signal, and lack of such hybridization to intron probes will yield a negative signal, providing a spatially ordered map of the expressed sequences in a portion of a genome (see the specification at, *e.g.*, Figure 1). As a result, the claimed positionally-addressable ordered arrays, when hybridized to mRNA or cDNA, yield not only information regarding the expression state of a gene of interest, but provide information regarding the location of an expressed gene in a given genomic sequence and location of exons, introns and intron-exon boundaries within such gene with high resolution. It is the claimed combination of the recited features of the arrays of the Applicants' invention, *i.e.*, high density, large span and Exclusively Intron Probes in a positionally-addressable ordered array, that enable such arrays to map expressed genes and assess the intron/exon structure of the expressed genes in genomic sequences that are spread over large regions of genomic DNA (*i.e.*, at least over 25,000 bp). Thus, the claimed combination of the recited features gives rise to a new function that is not afforded by the disparate disclosures of Lockhart, Bowtell, Hui and Ashe cited by the Examiner.

In the outstanding Office Action, the Examiner again relies on Bowtell for the large span of the Applicants' claims, on Lockhart for the high density of the claims, and on Hui for allegedly teaching the Exclusively Intron Probes of the claims. The Examiner, however, for the first time, also relies on Ashe for allegedly teaching the Exclusively Inron Probes, and specifically for teaching "detection of genes in the gene structure of a plasmid using gene-specific intron probes" (see Office Action at page 12). The Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the arrays of Lockhart and Bowtell by including intron probes as suggested by Hui and Ashe (see Office Action at page 13). The Examiner further alleges that the motivation to do so is provided by Hui who teaches intron probes for gene detection and Ashe who teaches that gene-specific intron probes can be used to detect a gene in a plasmid structure (see Office Action at page 13).

There is no discernible reason that would have prompted a person of ordinary skill in the relevant field to combine the elements disclosed in Bowtell, Lockhart, Ashe and Hui in the way the Applicants' claimed invention does. *Cf. KSR*, S.Ct. at 1741, 82 U.S.P.Q.2d at

1396. In fact, one of ordinary skill in the art would not have combined these references because, among other reasons, the probes disclosed in these references are designed for hybridization with entirely different target materials as explained in detail below. Because all probes of an array are meant to be hybridized with the same target material, one of ordinary skill in the art would not have placed probes taught in the references cited by the Examiner on the same array.

Bowtell discloses use of microarray probes, representing expressed sequences—ORFs, cDNAs or ESTs—to analyze expression of genes into proteins, wherein the probes span a large region of the genomic sequence (see Bowtell at page 29, Table 3, columns 1 and 2). Thus, Bowtell's arrays have the feature of a large span, but not the high density or Exclusively Intron Probes of the array of the Applicants' claims. Bowtell is interested only in detection of expressed genes. The Examiner cites to page 25 of Bowtell for the teaching of RNA expression analysis in Bowtell (see Office Action at page 8). Precisely, Bowtell is interested in RNA expression (*i.e.*, translation or expression into proteins), and not in nascent transcription into primary RNA with which Ashe is concerned (because Ashe is interested in detection of sequences that are not expressed as proteins as further explained below). In order to detect RNA expression into proteins, Bowtell uses protein-coding target molecules, *e.g.*, cDNA or mRNA (see Bowtell at, *e.g.*, p. 26, left col., 1st para). There is no common sense reason to contact the arrays of Bowtell with genomic DNA or primary RNA, because contacting the arrays of Bowtell with such target molecules will not yield information about whether sequences of the probes are expressed into proteins.

Lockhart discloses use of high density tiling arrays to determine whether a given gene possesses a sequence signature of up to 300 nucleotides or up to 300 amino acids in order to obtain information about the given gene, *e.g.*, to determine whether it encodes a member of a gene family or comprises a sequence from one of a set of genes (see Lockhart at Abstract, column 1, lines 50-59 and column 7, line 10 to column 8, line 12). Some of Lockhart's sequence signatures are "coding," *i.e.*, expressed into proteins, and some are "non-coding," *i.e.*, not expressed into proteins. There is no common sense reason to contact non-coding sequence signature probes with cDNA or mRNA target molecules, which encode proteins; rather, such non-coding sequence signature probes would be contacted with genomic DNA or primary RNA target molecules, because non-coding regions are more predominant in genomic DNA and primary RNA than in mRNA or cDNA. Thus, the probes of Bowtell and the non-coding sequence signature probes of Lockhart would not be placed on the same array

because they would be contacted with different target molecules in order to perform their respective functions. Coding sequence signature probes of Lockhart, on the other hand, would be contacted with mRNA or cDNA. However, even though the probes of Bowtell and the coding sequence signature probes of Lockhart would still fulfill their functions if placed on the same array, one of ordinary skill in the art would not have combined such probes with another element of the Applicant's claims, the Exclusively Intron Probes, as further explained below.

Ashe teaches use of Nuclear run-on analysis ("NRO") and in situ hybridization to study transcription of the locus control region ("LCR") and intergenic regions in the human β-globin locus (Ashe at Abstract and p. 2494). The Examiner specifically cites to the last full paragraph on p. 2503 and Figure 9, where Ashe describes use of gene-specific intronic probes to detect plasmid transcription using an in situ hybridization assay (see Office Action at p. 12). Regarding the in situ hybridization experiments disclosed by Ashe, Applicants firstly point out that the in situ hybridization technique is radically different from an array, the subject matter of the Applicants' claimed invention. In situ hybridization does not involve using an array of probes, *i.e.*, binding the probes to a solid support; instead, during in situ hybridization, the probes, in soluble form and unbound to a solid support, are incubated with fixed cells bound to slides before washing the slides (see Ashe, "In situ hybridization" section at p. 2507), which is consistent with the goal of in situ hybridization – to localize transcripts in cells (see p. 2503, last paragraph). It would be counter to common sense to put in situ hybridization probes on an array because such would fail to provide any localization data. Further, in situ hybridization disclosed in Ashe entails binding of the probes to the fixed cells containing the total pool of RNA in the cell (see p. 2507). Regarding the NRO experiments disclosed by Ashe, they also entail binding of probes to the total pool of RNA isolated from nuclei (see p. 2506, last paragraph). Indeed, the function of the gene-specific intron probes of Ashe is to detect gene-specific transcription of such non-coding regions into primary RNA, which is only possible using a biological sample containing primary, unprocessed RNA and not mRNA or cDNA, which only detect sequences expressed into proteins. Ashe provides no motivation to hybridize its intron probes to mRNA or cDNA because Ashe is interested in detection of all regions that get transcribed, even intron regions, which cannot be detected with mRNA or cDNA. In other words, Ashe is interested in sequences that are transcribed, regardless of whether they are translated. Thus, the probes of Ashe and the probes taught in

Bowtell would not be on the same array because they must be contacted with different target molecules in order to fulfill their respective functions.

Hui is interested in diagnosing mutations in one specific gene: the von Hippel-Lindau ("VHL") tumor suppressor gene. Hui discloses oligonucleotides complementary to intron regions of the VHL tumor suppressor gene for use as amplification and sequencing primers in the diagnosis of VHL gene mutations (see Hui at col. 3, line 8 to col. 4, line 16). Hui does not teach or suggest that such oligonucleotides complementary to intron regions are immobilized on an array. Hui also teaches use of a panel of probes for various known mutations in the VHL tumor suppressor gene immobilized as an array to be probed with patient DNA (see Hui at col. 10, lines 52-54). Hui does not teach that probes to mutations in the VHL intron sequences be used. As in Ashe, even assuming *arguendo* that Hui teaches intron probes, such probes of Hui must be hybridized to patient's genomic DNA or primary RNA because such sequences cannot be detected with mRNA or cDNA. Thus, such probes of Hui and the probes taught in Bowtell would not be on the same array because they will have to be contacted with different target molecules.

Bowtell provides no reason to combine the large span of its arrays with high density of arrays of Lockhart and intron probes of Hui and Ashe, because the purpose of Bowtell is to determine whether genes are expressed into proteins. The sequences of expressed genes are interrupted by non-coding sequences, *e.g.*, intron sequences, which are not expressed into proteins and, thus, are irrelevant for the purposes of Bowtell. Bowtell provides no common sense reason to tile at high density throughout large genomic sequences using Exclusively Intron Probes because doing so will not facilitate detection of protein expression. Further, one of ordinary skill in the art would simply not have placed (i) the probes to coding sequences of Bowtell, and (ii) the intron probes of Ashe or Hui or non-coding sequence signature probes disclosed in Lockhart, on the same array because such probes would be contacted with different target molecules in order to accomplish their respective functions. Intron probes and non-coding sequence signature probes would be hybridized to primary RNA or genomic DNA sequences, not to cDNA or mRNA. Use of intron probes or non-coding sequence signature probes disclosed in Lockhart in the arrays of Bowtell would render such probes inoperable for the intended purpose of Bowtell and inoperable for the provision of any useful information. *See In re Gordon*, 221 U.S.P.Q. at 1127. Intron probes would not hybridize to mRNA and cDNA targets with which expression arrays are contacted, and thus yield no information about protein expression (with which Bowtell is concerned). Non-

coding sequence signature probes of Lockhart would not be contacted with mRNA or cDNA because non-coding regions are more predominant in genomic DNA and primary RNA than in mRNA or cDNA. Thus, it would be counter to common sense to place intron probes of Ashe or Hui or non-coding sequence signature probes of Lockhart on the same array with the probes of Bowtell, because such would be contacted with different target molecules.

Further, Lockhart provides no reason to combine its high density tiling arrays with the large span of arrays of Bowtell, because the purpose of Lockhart is to identify signature sequences. There is no disclosure in Lockhart of sequence signatures longer than 300 nucleotides or 300 amino acids, and thus, Lockhart provides no common sense reason to tile at high density throughout large genomic sequences (*e.g.*, at least 25,000 bp) because doing so will not facilitate identification of sequence signatures. Furthermore, in its "coding" embodiments, where Lockhart teaches probing for signature sequences in expressed protein sequences, it would be nonsensical to use Exclusively Intron Probes which do not recognize any coding sequences. Doing so would render the Exclusively Intron Probes inoperable for the intended purpose of such arrays of Lockhart, because intron probes do not hybridize to and yield no information about coding sequences. *See In re Gordon*, 221 U.S.P.Q. at 1127. Thus, one of ordinary skill in the art would not combine the coding sequence signature probes of Lockhart with the intron probes of either Ashe or Hui. In fact, Lockhart provides no motivation to place its coding sequence signature probes and its non-coding sequence signature probes on the same array because such different embodiments would have to be contacted with different target molecules. On the other hand, the "non-coding" embodiments of Lockhart, in which Lockhart teaches tiling across sequence signatures that are not expressed as proteins, have no relevance to and cannot properly be combined with the teachings of Bowtell, which deals solely with protein expression analysis, as described above. Taken together, the disparate elements disclosed in Bowtell, Lockhart, Hui and Ashe would not have been combined by one of ordinary skill in the art. The reasons why the disparate probes of the cited references cannot properly be combined to achieve the claimed invention can be readily appreciated by reference to the Table A below:

Table A

Arrays of	Would one contact with mRNA/cDNA?
Bowtell	Yes
Lockhart, coding sequence signatures	Yes
Lockhart, non-coding sequence signatures	No
Ashe	No
Hui	No

Applicants urge the Examiner to consider the claimed invention as a whole. See M.P.E.P. 2141.02 (I). Applicants also urge the Examiner not to use hindsight reconstruction to pick and choose among the isolated disclosures of the prior art to deprecate the claimed invention. See *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir. 1988). It is the Applicants' invention, and not the disclosures of Lockhart, Bowtell, Hui or Ashe, that for the first time provides the common sense reason to combine the claimed elements in the manner recited in the Applicants' claims. It was the inventors of the present invention who recognized that the claimed combination of the recited elements, such as large span, high density and Exclusively Intron Probes in positionally-addressable ordered arrays, gives rise to a new function that is not afforded by Bowtell, Lockhart, Hui and Ashe relied on by the Examiner. As discussed above, the claimed arrays provide a high throughput method to map the genes in the genome, to determine the exon/ intron structure of genes and to precisely identify the boundaries of expressed genes in genomic sequences without extensive DNA sequencing of ESTs (see specification at page 3, lines 13-28 and page 4, lines 1-21). In order to facilitate such gene mapping, an array must have probes spanning a large portion of a genomic sequence, at high density, contain probes to intron sequences and be positionally-addressable and ordered, the features recited in the Applicants' claims. Further, the Applicants' claimed invention provides the only common sense reason to combine intron probes and exon tiling probes in one array, because it provides a reason to hybridize intron probes, *i.e.*, Exclusively Intron Probes of the claims, as well as exon probes, to mRNA or cDNA target molecules, since the purpose of such hybridization is not detection of intron sequences but mapping/spatial positioning of the expressed exon sequences. There is no other reason that would have motivated one of ordinary skill in the art to combine the

disparate features of large span, high density and Exclusively Intron Probes in a positionally-addressable ordered array. Taken as a whole and without hindsight, the Applicants' claimed invention is non-obvious over the references cited by the Examiner.

Based on the foregoing, one of ordinary skill in the art would not be prompted to combine the teachings of Lockhart, Bowtell, Ashe and Hui. As set forth in *KSR*, it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does...." *KSR*, S.Ct. at 1741, 82 U.S.P.Q.2d at 1396. In the instant case, such a reason is not present. To the contrary, as explained above, there is reason not to combine the individual elements of the cited references in the manner proposed by the Examiner.

Furthermore, it is evident that the arrays of the claims are "more than the predictable use of prior art elements according to their established functions." *See KSR*, 127 S.Ct. at 1740 (citing *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57 (1969) and *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273 (1976)). As discussed above, the prior art elements cannot be contacted with the same type of nucleic acid target molecules as they would be if present on the same array, and still work according to their established functions. Thus, the claimed invention does not employ known elements according to their established functions.

Therefore, claims 122, 185, 189, 192, 197, 200, 221-222, 224, 226 and 228-232 are not made obvious by Lockhart, Bowtell, Hui and Ashe, and the rejection of these claims should be withdrawn.

C. Claim 223 Is Patentable Over Lockhart, Bowtell, Hui and Ashe, in View of Schena

Finally, with respect to claim 223, the Examiner relies on Schena for its disclosure of microarrays to measure expression of plant genes to support the alleged obviousness of claim 223 (Office Action at page 15). Specifically, the Examiner asserts that it would have been obvious to one skilled in the art to modify the array of Lockhart, Bowtell and Hui by targeting nucleotide sequences of plant genes as suggested by Schena because Schena teaches usefulness of microarrays in measuring plant genes and Lockhart, Bowtell and Hui teach the detection of genes and gene mutations using arrays and microarrays (Office Action at page 16). Further, the Examiner asserts that motivation to do so is provided by Ashe who generally teaches that plant genomic sequences should be analyzed in the same way as

humans and Drosophila, and teaches that intron probes can detect genes and their structure in animals (Office Action at page 16).

Claim 223 is not obvious over Bowtell, Lockhart, Hui, Schena and Ashe by virtue of its dependency on claim 122, which is not obvious over any of these references alone or in combination, for the reasons discussed above. Applicants point out that Schena suffers from the same deficiencies as Bowtell, and there is no discernible reason that would have prompted a person of ordinary skill in the art to combine Schena with Lockhart, Hui and Ashe to create an array with a probe set having the long span, high density, and at least two probes that are hybridizable to genomic sequences contained entirely within an intron in a positionally-addressable ordered array, as specified in the Applicants' claims.

Like Bowtell, Schena is directed to the analysis of gene expression into proteins, in Schena's case using cDNAs as probes. Schena is concerned with the use of microarrays containing 1046 random human cDNA clones from a library of Epstein-Barr virus-transformed human peripheral blood lymphocytes, with 10 *Arabidopsis* clones as controls, for monitoring gene expression into proteins (see Schena at page 10614, under "Materials and Methods"). Schena also discloses use of microarrays of cDNA clones to measure expression of plant genes (see Schena at page 10614, left column).

There is no reason based on Schena to probe for intron sequences. Contrary to the Examiner's assertion that Schena broadly teaches in the 1st sentence on page 10614 [*sic*, 2nd sentence on page 10614] the analysis of complete genome sequences by probes which necessarily include introns (Office Action at page 15), Schena simply states, in the sentence cited by the Examiner, that "complete genome sequences for all of the model organisms and human will probably be available by the year 2003." This sentence is not a teaching of "probes that necessarily include introns." Rather, as would be well apparent to one of ordinary skill in the art, this sentence refers to sequencing of the human genome. There is no reason why genomic sequencing would suggest the use of intron probes on an array to one of ordinary skill in the art, nor does the Examiner explain why it would do so. Again, Schena is concerned with analysis of gene expression into proteins, and such analysis is undoubtedly facilitated by having "complete genome sequence for all of the model organisms and human." However, just because a genome is sequenced does not mean that one of ordinary skill in the art would have been motivated to include Exclusively Intron Probes on an array. There must be a reason to include such probes on an array. Schena fails to provide such a reason,

because Schena is only concerned with analysis of gene expression into proteins, where Exclusively Intron Probes or high density tiling using such probes would not serve any useful purpose. Further, and as described in detail in the response filed on February 26, 2009, using probes contained entirely within an intron in the arrays of Schena would render the Exclusively Intron Probes inoperable for the intended purpose of Schena and for providing any useful function, because intron probes do not hybridize to the protein-coding sequences with which expression arrays are contacted, and thus do not detect gene expression into proteins. As described above, intron probes detect complementary sequences in primary RNA transcripts or genomic DNA, not mRNA or cDNA. One of ordinary skill in the art would simply not have placed the probes of Schena and the probes of Ashe or Hui or non-coding sequence signature probes disclosed in Lockhart on the same array because such probes would be contacted with different target molecules in order to accomplish their respective functions. Schena's probes would be contacted with mRNA or cDNA like those of Bowtell, whereas probes of Ashe or Hui and non-coding probes of Lockhart would be contacted with primary RNA or genomic DNA as illustrated in the Table B below.

Table B

Arrays of	Would one contact with mRNA/cDNA?
Schena	Yes
Bowtell	Yes
Lockhart, coding sequence signatures	Yes
Lockhart, non-coding sequence signatures	No
Ashe	No
Hui	No

Thus, it would be counter to common sense to place intron probes of Ashe or Hui or non-coding sequence signature probes of Lockhart on the arrays of Schena or Bowtell. There is no other reason that would motivate one of ordinary skill in the art to combine Bowtell, Schena, Lockhart, Hui and Ashe, for the same reasons as discussed above. Therefore, claim

223 is not made obvious by Lockhart, Bowtell, Hui, Schena and Ashe, and the rejection of claim 223 should be withdrawn.

In view of the foregoing remarks, it is submitted that the obviousness rejections are in error and should be withdrawn.

II. CLAIMS WITHDRAWN FROM CONSIDERATION AS BELONGING TO NON-ELECTED SPECIES SHOULD BE CONSIDERED

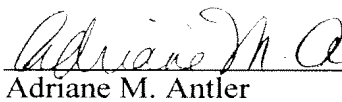
Claims 186-188, 190-191, 193-196, 198-199, 201-220, 225 and 227 were withdrawn from consideration by the Examiner as belonging to non-elected species. Since Applicants believe that the generic claims are allowable, claims 186-188, 190-191, 193-196, 198-199, 201-220, 225 and 227 should be considered by the Examiner. Applicants respectfully request that these claims be considered by the Examiner.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks into the file of the above-identified application. Applicants respectfully request that the Examiner reconsider this application with a view towards allowance. The Examiner is invited to call the undersigned attorney if a telephone call would help resolve any remaining items.

Respectfully submitted,

Date: September 10, 2009



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